

# Nutrition and Metabolism Panels

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## **Guidelines**

### **Nutrition and Metabolism Panels**

Nutrition is essential to good health, is involved in all metabolic processes, and is an important determinant of a number of illnesses. The field of nutrition, therefore, is necessarily broad in scope. Nevertheless, to be more effective in promoting a focused effort on the most important, contemporary, nutrition-related health problems in the United States, Japan, and Southeast Asia, the major research objectives of the Panels are as follows:

1. Obesity, diabetes, and related metabolic disorders: (a) recognition of relationships between body fat distribution and nutrition, diabetes, dyslipidemias, and atherosclerosis and (b) investigation of the increasing prevalence of diabetes, dyslipidemias, and atherosclerosis in all nations of the world, especially the recent rapid increases in Asia
2. Metabolic bone disease: emphasis on the importance of metabolic bone disease and its debilitating effects in countries having populations with low calcium intake, such as Japan, and studies of the increasing prevalence of osteoporosis in all countries as the population ages
3. Nutrition and host defense: attention to the associations between nutrition and host defenses, which are involved in response to infection, trauma, inflammatory disease, and neoplasia

These research objectives continue to reflect major problems throughout the world, as trends toward overnutrition, malnutrition, and aging of the population accelerate.

## Five-Year Summary

### Broad Goals

The Nutrition and Metabolism Panels recognize that nutrition-related disorders remain serious concerns in the United States, Japan, and throughout the world. The consequences of changing lifestyles, dietary patterns, and food habits are of considerable concern to the Panels. Dietary patterns are known to be contributing variables or risk factors for a number of chronic diseases. Efforts to promote collaborative studies between U.S. and Japanese scientists have resulted in findings that reveal relationships between dietary components and chronic diseases, and these efforts will continue.

The Nutrition and Metabolism Panels will work to foster scientific studies directed toward (1) a better understanding of the relationships between nutrition and susceptibility to disease, disease progression, and outcome; (2) elucidation of the mechanisms involved at the gene, molecular, and cellular levels; and (3) identification and investigation of new strategies for prevention and therapy. To accomplish these goals, the Panels support several scientific approaches, including nutritional epidemiology, molecular genetics and cellular biology, and clinical investigations. The broad goals relate to both undernutrition and overnutrition and focus on the critical issue of the effects of changes in nutrition and metabolism on disease expression, progression, and prognosis.

The Panels also continue to promote collaborative studies between U.S. and Japanese scientists, which have been successful in revealing relationships between dietary components and chronic disease. They anticipate that such research will continue to be presented at Panel conferences and

will serve as the focus for development of more extensive interactions between young investigators and more established investigators from the United States and Japan. Such interactions are expected to become even more effective and extensive in the future. Opportunities for frequent international meetings and visits continue to have high priority.

### Progress and Accomplishments

During the past 5 years, much has been accomplished in understanding the molecular and genetic bases of nutrition-related diseases. Panel activities not only have focused on annual meetings and conferences but have also resulted in a number of laboratory and clinical interactions among Panel members and other investigators from the United States and Japan on several fronts of scientific investigation. Active collaborations continue between Panel scientists and other scientists from both countries in virtually all the Panels' priority areas of research, from the bench to the bedside. Examples of these joint efforts are presented here.

Longitudinal studies of risk factors for development of non-insulin-dependent diabetes mellitus (type 2 diabetes) and cardiovascular disease in older second-generation and younger third-generation Japanese have been under way for a number of years. These studies also include examination of risk factors for other diseases in Japanese-American families, collection of genetic material for future study, and examination of the effects of lifestyle interventions (diet and exercise) on risk factors for type 2 diabetes in persons with impaired glucose tolerance (IGT). The studies first revealed that the prevalence of type 2 diabetes has increased at a greater rate in Japanese Americans than in native

Japanese. The prevalence of IGT has also increased among Japanese Americans, and there is a high rate of conversion from IGT to type 2 diabetes. Furthermore, there is a higher prevalence of coronary heart disease and hypertension in persons with both IGT and type 2 diabetes. Related collaborative studies are addressing the molecular basis and pathophysiology of familial combined hyperlipidemia.

A major joint effort between U.S. and Japanese investigators focused on cloning the 25-hydroxyvitamin D<sub>1</sub>  $\alpha$ -Oase (25-OH-D<sub>1</sub>  $\alpha$ -Oase). This is the key enzyme that produces the vitamin D hormone, and it is tightly regulated by the need for calcium and phosphorous. This joint research effort by U.S. and Japanese scientists led to successful cloning of the cDNA (complementary DNA) for the rat 25-OH-D<sub>1</sub>  $\alpha$ -Oase. Using this information, these investigators were successful in cloning the gene encoding 1 $\alpha$ -hydroxylase, including the promoter. They further determined the full structure of the mouse enzyme, isolated the promoter, and revealed that it has the parathyroid-sensitive site. These collaborations will hopefully lead to a full definition of the molecular mechanism by which parathyroid hormone activates the production of the vitamin D hormone.

Other cooperative studies have focused on the structure of the vitamin D receptor protein. Japanese scientists have synthesized fluoro derivatives of 1 $\alpha$ ,25-dihydroxy-vitamin D<sub>3</sub> and have performed fluorine nuclear magnetic resonance studies with this probe. Collaborating U.S. investigators have expressed the ligand-binding domain of the vitamin D receptor by PET-14A gene expression, and they provide homogeneous protein with a ligand-binding domain for the nuclear magnetic resonance studies. These studies are expected to elucidate the

structure-function relationships and the binding pocket for the vitamin D hormone in the receptor.

Other collaborations focus on analogues of the vitamin D hormone synthesized in Japan. U.S. scientists are testing these compounds for the ability to bind to the vitamin D receptor, to influence cellular differentiation, to elevate serum calcium, and to stimulate calcium transport activity.

In extensive joint efforts, U.S. and Japanese researchers are investigating the development of obesity and related type 2 diabetes, with particular attention to novel adipose-specific genes and their significance. Among these is an unknown gene that appeared in the cDNA library for adipose tissue but never in other cDNA libraries. The cDNA encoded a collagen-like protein, which the researchers named adiponectin. In vitro studies revealed that adiponectin is bound to collagens present in vascular subendothelial space and that it attenuated proliferation of vascular smooth muscle cells that was stimulated by growth factor. These researchers reported that the plasma level of adiponectin is markedly decreased in obese persons, and the findings indicate that the paradoxical decrease of plasma adiponectin in obesity may play a role in the development of vascular disease. U.S. and Japanese investigators are working together to examine the expression and regulation of adiponectin in obese, nonhuman primates.

Collaborative studies to define the molecular defects in patients with

genetic disorders of lipoprotein metabolism identified in the United States and Japan have been under way for a number of years. One study focused on attempts to determine the frequency of familial defective apolipoprotein B-100 (FDB) in patients with hypercholesterolemia who attended a lipid specialty clinic in Japan. Blood samples from U.S. patients with a diagnosis of FDB were sent to investigators in Japan, who established the polymerase chain reaction assay for FDB and validated the assay in control subjects known to have FDB. The clinical presentation of FDB is similar to that of hypercholesterolemia, but the assay revealed an absence of defective apolipoprotein in the patients with hypercholesterolemia.

## Future Goals

The Panels consider the three priority research areas to be essential for improved understanding of the relationships between nutrition and chronic diseases (see section on Guidelines), and annual symposia serve as an important stimulus for interactions and exchange of information. These efforts continue, as young U.S. and Japanese scientists develop professional relationships to investigate critical interactions between nutrition and disease. To accomplish their scientific goals, the Panels support the following approaches:

1. Nutritional epidemiology: Comparative studies of diet, nutrition, and the incidence, progression, and severity of disease can help to elucidate the role of diet in the etiology of chronic disease states.

These studies focus on factors such as the nature and quantity of lipids, total energy, vitamins and minerals, and antioxidants in the diet.

Epidemiologic studies of nutrition also can identify potential relationships between nutrition and disease expression and can help to focus studies on the mechanisms involved.

2. Molecular genetics and cellular biology: To understand the mechanisms by which nutrition influences the expression of disease, it is necessary to clarify how nutrition alters gene expression at the molecular level and cellular response at the physiological level. This effort requires studies on pathways of regulation at the transcriptional and translational levels, mechanisms of cell signaling and signal transduction, the roles of cytokines, and cell metabolism and physiological responses in in vitro cell and cell-free systems and in animal models.

3. Clinical investigations: An essential component of clinical research on nutrition is well-designed studies in relatively small numbers of carefully chosen, well-characterized persons. The Nutrition and Metabolism Panels work to promote efforts to address differences in susceptibility and heterogeneity of responses determined by differences in nutrient consumption. Intervention studies in these "human models" are expected to help in defining appropriate population-based intervention trials.

## Selected References

Chang MY, Potter-Perigo S, Tsoi C, Chait A, Wight TN. Oxidized low density lipoproteins regulate synthesis of monkey aortic smooth muscle cell proteoglycans that have enhanced native low density lipoprotein binding properties. *J Biol Chem* 2000;275:4766-73.

Chua SC, Chung WK, Wu-Peng S, Shun-Mei Liu L, Tartaglia R, Leibel R. Phenotypes of mouse (diabetes) and rat (fatty) due to mutations in the OB (leptin) receptor. *Science* 1996;271:994-6.

Keusch GT. The potential impact of nutritional change on the global burden of viral diseases. *Nutr Rev* 2000;58 (2 Pt 2):S55-S62.

Lee G-H, Proenca R, Montez JM, Carroll KM, Darvishzadeh JG, Lee JI, Friedman JM. Abnormal splicing of the leptin receptor in diabetic mice. *Nature* 1996;379:632-5.

Yamamoto K, Masuno H, Choi M, Nakashima K, Taga T, Ooizumi H, Umesono K, Sicinska W, VanHooke J, DeLuca HF, Yamada S. Three-dimensional modeling of and ligand docking to vitamin D receptor ligand binding domain. *Proc Natl Acad Sci USA* 2000;97:1467-72.